

CLAIMS

We claim:

1. A crystal comprising a polypeptide which includes an extracellular domain of a receptor protein tyrosine kinase.
2. The crystal of claim 1 wherein the extracellular domain comprises one or more Ig-like domains.
3. The crystal of claim 2, wherein the receptor protein tyrosine kinase is a fibroblast growth factor receptor.
4. The crystal of claim 3, wherein the extracellular domain comprises Ig-like domain 2 and Ig-like domain 3 and does not comprise Ig-like domain 1.
5. The crystal of claim 1, wherein the fibroblast growth factor receptor is fibroblast growth factor receptor 1.
6. The crystal of claim 1, wherein polypeptide comprises amino acid residues 142-365 of fibroblast growth factor receptor 1.
7. The crystal of claim 1, wherein the polypeptide comprises amino acid residues 150-360 of FGFR1 having the sequence shown in Figure 4.
8. The crystal of claim 1 further comprising a ligand bound to the receptor protein tyrosine kinase.
9. The crystal of claim 8 wherein the receptor protein tyrosine kinase is fibroblast growth factor receptor 1 and the ligand is FGF1.
10. The crystal of claim 9 wherein FGF1 has an amino acid sequence as shown in Figure 17.
11. The crystal of claim 9 defined by the atomic structural coordinates of Table 2.

12. The crystal of claim 11 belonging to the tetragonal space group P1, and having unit cell dimensions of  $a=b=98.5 \text{ \AA}$ ,  $c=197.0 \text{ \AA}$ .
13. The crystal of claim 8, wherein the receptor protein tyrosine kinase is fibroblast growth factor receptor 1 and the ligand is FGF2.
14. The crystal of claim 13 wherein FGF2 has an amino acid sequence as shown in Figure 17.
15. The crystal of claim 13 defined by the atomic structural coordinates of Table 1.
16. The crystal of claim 13 belonging to the tetragonal space group P41212, and having unit cell dimensions of  $a=62.55 \text{ \AA}$ ,  $b=64.06 \text{ \AA}$ ,  $c=64.14 \text{ \AA}$ ,  $\alpha=93.40^\circ$ ,  $\beta=111.17^\circ$ , and  $\gamma=97.18^\circ$ .
17. The crystal of claim 1 further comprising at least one heavy atom.
18. A three-dimensional representation of the structure of the extracellular domain of claim 1 or 8.
19. The crystal of claim 1 or 8 wherein the receptor protein tyrosine kinase is a mutant receptor protein tyrosine kinase.
20. The crystal of claim 8 wherein the ligand is a mutant ligand.
21. The crystal of claim 1 wherein the fibroblast growth factor receptor is fibroblast growth factor receptor 2.
22. The crystal of claim 21 wherein polypeptide comprises amino acid residues 147-366 of fibroblast growth factor receptor 2.
23. The crystal of claim 22 wherein polypeptide comprises an amino acid sequence for fibroblast growth factor receptor 2 residues 150-360 as shown in Figure 4.
24. The crystal of claim 8 wherein the receptor protein tyrosine kinase is fibroblast growth factor receptor 2 and the ligand is FGF2.

25. The crystal of claim 24 wherein FGF2 has an amino acid sequence as shown in Figure 17.
26. The crystal of claim 24 defined by the atomic structural coordinates of Table 3.
27. The crystal of claim 24 belonging to the triclinic space group P1, and having unit cell dimensions of  $a=72.20 \text{ \AA}$ ,  $b=71.68 \text{ \AA}$ ,  $c=90.92 \text{ \AA}$ ,  $\alpha=90.53^\circ$ ,  $\beta=89.98^\circ$ , and  $\gamma=89.99^\circ$ .
28. A crystal comprising a polypeptide that includes a receptor binding core of a stem cell factor.
29. The crystal of claim 28 wherein the receptor binding core of the polypeptide comprises a four-helix bundle.
30. The crystal of claim 29 wherein the receptor binding core of the polypeptide further comprises two  $\beta$  strands.
31. The crystal of claim 30 comprising a homodimer of the polypeptide.
32. The crystal of claim 31 comprising a non-covalent homodimer of the polypeptide.
33. The crystal of claim 32 wherein said crystal is orthorhombic and has unit cell dimensions  $a = 72.47 \text{ \AA}$ ,  $b = 83.45 \text{ \AA}$  and  $c = 89.15 \text{ \AA}$ .
34. The crystal of claim 33 wherein said crystal is monoclinic.
35. The crystal of claim 34 defined by the atomic structural coordinates of Table 4.
36. The crystal of claim 32 comprising a non-covalent homodimer of a polypeptide including amino acid residues 1-141 of the stem cell factor.
37. The crystal of claim 32 wherein the non-covalent homodimer has C2 symmetry.
38. The crystal of claim 29 further comprising a ligand bound to the receptor binding core.
39. The crystal of claim 38 wherein the ligand is a receptor protein tyrosine kinase.

40. The crystal of claim 39 wherein the receptor protein tyrosine kinase is a *c-kit* polypeptide.
41. A three-dimensional representation of a structure of a polypeptide which includes a receptor binding core of a stem cell factor.
42. The three-dimensional representation of claim 41 in computer readable form.
43. A computer based system for depicting and analyzing a molecular structure which comprises a polypeptide which includes an extracellular domain of a receptor protein tyrosine kinase, said system comprising:
- (a) a data storage device storing structural data from the molecular structure;
  - (b) a computer processor coupled to said memory, said processor generating processed output on said data using a set of programmed instructions; and
  - (c) a display device coupled to said processor, said display rendering multi-dimensional images of the molecular structure according to said processed output.
44. The system of claim 43, wherein said data storage device comprises:
- (i) at least one first-type storage region comprising a set of spatial coordinates of the molecular structure in a multi-dimensional space; and
  - (ii) at least one second-type storage region comprising a representation of characteristics of a plurality of amino acids of the molecular structure,
- wherein said second-type storage region is logically associated with said first-type storage region to support data processing in said processor.
45. The system of claim 43, wherein said processor (i) accesses the structural data in said memory, and (ii) generates image signals for depicting a visual image of the molecular structure in a multi-dimensional space corresponding to a set of structural data points in said data storage device, and wherein said image signals are the processed output.
46. The system of claim 43, wherein said display (i) receives said processed output, and (ii) renders a visual image of said molecular structure on a computer screen according to said processed output.

47. The system of claim 43, further comprising:
- (i) a storage device for storing data of geometric arrangements of characteristics of a composition other than the molecular structure, wherein said storage device is coupled to said processor; and
  - (ii) an operator interface for receiving instructions from an operator, wherein said interface is coupled to said processor,
- wherein said processor generates additional image signals for depicting a visual representation of said composition relative to the visual image of said polypeptide, according to said instructions from the operator interface, said additional image signals being the additional processed output.
48. The system of claim 43, wherein the structural data are set forth in Table 1, 2, 3 or 6.
49. A memory that stores information for generating a visual display of a a molecular structure which comprises a polypeptide which includes an extracellular domain of a receptor protein tyrosine kinase, said memory comprising:
- (i) at least one first-type storage region, comprising a set of spatial coordinates of the molecular structure in a multi-dimensional space; and
  - (ii) at least one second-type storage region, comprising a representation of a characteristic of a plurality of amino acids of the molecular structure;
- wherein said second-type storage region is associated with said first-type storage region to represent a geometric arrangement of the molecular structure in a multi-dimensional space.
50. The memory of claim 49, wherein said second-type storage regions are logically associated with said first-type storage regions to represent a geometric arrangement of at least one characteristic of the extracellular domain of the molecular structure in a multi-dimensional space.
51. The memory of claim 50, wherein the spatial coordinates are set forth in Table 1, 2, 3 or 6.

52. A computer based system for depicting and analyzing a molecular structure which includes a stem cell factor or portion thereof, comprising:
- (a) a data storage device storing structural data from the molecular structure;
  - (b) a computer processor coupled to said memory, said processor generating processed output on said data using a set of programmed instructions; and
  - (c) a display device coupled to said processor, said display rendering multi-dimensional images of the molecular structure according to said processed output.
53. The system of claim 52, wherein the molecular structure comprises a polypeptide which includes a stem cell factor receptor binding core.
54. A method of determining a three dimensional structure of a receptor protein tyrosine kinase extracellular domain of unknown structure, the method comprising:
- (a) aligning an amino acid sequence of the receptor protein tyrosine kinase extracellular domain of unknown structure with an amino acid sequence of a receptor protein tyrosine kinase extracellular domain having known atomic structural coordinates, wherein the alignment is achieved by matching homologous regions of the amino acid sequences;
  - (b) transferring a computer representation of each of the homologous amino acids from the known atomic structural coordinates to a computer representation of a structure of the corresponding amino acids in the receptor protein tyrosine kinase extracellular domain of unknown structure to provide a receptor protein tyrosine kinase extracellular domain structure; and
  - (c) determining the three dimensional structure of the receptor protein tyrosine kinase extracellular domain of unknown structure by determining a low energy conformation of the resulting receptor protein tyrosine kinase extracellular domain structure.
55. A method of determining a three dimensional structure of a receptor protein tyrosine kinase extracellular domain of unknown structure, the method comprising:
- (a) determining the positions of atoms in the unit cell of a crystal comprising the receptor protein tyrosine kinase extracellular domain of unknown structure by

matching a diffraction data set obtained from the crystal with a diffraction data set obtained from a crystal comprising a receptor protein tyrosine kinase extracellular domain having known atomic structural coordinates to provide a receptor protein tyrosine kinase extracellular domain structure; and

(b) determining the three dimensional structure of the receptor protein tyrosine kinase extracellular domain of unknown structure by determining a low energy conformation of the resulting receptor protein tyrosine kinase extracellular domain structure.

56. A method of determining a three dimensional structure of a receptor protein tyrosine kinase extracellular domain of unknown structure, the method comprising:

(a) determining the secondary structure of the receptor protein tyrosine kinase extracellular domain of unknown structure using NMR data; and

(b) determining the three dimensional structure of the receptor protein tyrosine kinase extracellular domain of unknown structure by simplifying the assignment of through-space interactions of amino acids using the atomic structural coordinates of a receptor protein tyrosine kinase extracellular domain having known atomic structural coordinates.

57. A three dimensional structure of a receptor protein tyrosine kinase extracellular domain determined using any one of the methods of claims 54 to 56.

58. A method of identifying a modulator of receptor protein tyrosine kinase function, the method comprising:

(a) providing a three dimensional representation of the atomic structural coordinates of a receptor protein tyrosine kinase and docking a computer representation of a compound, ligand, or ligand analog from a computer data base into a binding site on the receptor protein tyrosine kinase to provide a complex;

(b) determining a conformation of the complex with a favorable geometric fit and one or more favorable complementary interactions;

(c) identifying a compound, ligand, or ligand analog that best fits the receptor protein tyrosine kinase binding site as a potential modulator of receptor protein tyrosine kinase function;

(d) administering the potential modulator to cells;

- (e) comparing the level of receptor protein tyrosine kinase phosphorylation between cells not administered the potential modulator and cells administered the potential modulator; and
- (f) identifying the potential modulator as a modulator of receptor protein tyrosine kinase function based on the difference in the level of receptor protein tyrosine kinase phosphorylation.
59. A method of identifying a modulator of receptor protein tyrosine kinase function, the method comprising:
- (a) modifying a three dimensional representation of a receptor protein tyrosine kinase having a compound, ligand, or ligand analog bound to it to provide a complex, wherein the three dimensional representations of the compound, ligand, or ligand analog and the receptor protein tyrosine kinase are defined by atomic structural coordinates;
- (b) determining a conformation of the complex with a favorable geometric fit and one or more favorable complementary interactions;
- (c) identifying a modified compound, ligand, or ligand analog that best fits the receptor protein tyrosine kinase as a potential modulator of receptor protein tyrosine kinase function;
- (d) administering the potential modulator to cells;
- (e) comparing the level of receptor protein tyrosine kinase phosphorylation between cells not administered the potential modulator and cells administered the potential modulator; and
- (f) identifying the potential modulator as a modulator of receptor protein tyrosine kinase function based on the difference in the level of receptor protein tyrosine kinase phosphorylation.
60. A method of identifying a modulator of receptor protein tyrosine kinase function, the method comprising:
- (a) providing a three dimensional representation of a compound, ligand, or ligand analog complexed with a receptor protein tyrosine kinase, where the three dimensional representations of the compounds, ligands, or ligand analogs and the receptor PTK are defined by atomic structural coordinates;



- (b) searching a data base for a compounds, ligand, or ligand analog similar to the complexed compound, ligand, or ligand analog using a compound searching computer program;
- (c) identifying the compound, ligand, or ligand analog similar to the complexed compound, ligand, or ligand analog as a potential modulator of receptor protein tyrosine kinase function;
- (d) administering the potential modulator to cells;
- (e) comparing the level of receptor protein tyrosine kinase phosphorylation between cells not administered the potential modulator and cells administered the potential modulator; and
- (f) identifying the potential modulator as a modulator of receptor protein tyrosine kinase function based on the difference in the level of receptor protein tyrosine kinase phosphorylation.

61. A method of identifying a modulator of receptor protein tyrosine kinase function, the method comprising:

- (a) providing a three dimensional representation of a compound, ligand, or ligand analog complexed with a receptor protein tyrosine kinase, wherein the three dimensional representations of the compounds, ligands, or ligand analogs and the receptor protein tyrosine kinase are defined by atomic structural coordinates;
- (b) identifying the compound, ligand, or ligand analog as a potential modulator by replacing portions of the compound, ligand, or ligand analog complexed with the receptor protein tyrosine kinase with similar chemical structures from a data base using a compound construction computer program, wherein the representations of the compounds are defined by structural coordinates;
- (c) administering the potential modulator to cells;
- (d) comparing the level of receptor protein tyrosine kinase phosphorylation between cells not administered the potential modulator and cells administered the potential modulator; and
- (e) identifying the potential modulator as a modulator of receptor protein tyrosine kinase function based on the difference in the level of receptor protein tyrosine kinase phosphorylation.

62. A method of identifying a modulator of receptor protein tyrosine kinase function, the method comprising:

- (a) providing a three dimensional representation of the atomic structural coordinates of a receptor protein tyrosine kinase and docking a computer representation of a compound, ligand, or ligand analog from a computer data base into a binding site on the receptor protein tyrosine kinase to provide a complex;
- (b) determining a conformation of the complex with a favorable geometric fit and one or more favorable complementary interactions;
- (c) identifying a compound, ligand, or ligand analog that best fits the receptor protein tyrosine kinase binding site as a potential modulator of receptor protein tyrosine kinase function;
- (d) administering the potential modulator to cells;
- (e) comparing the level of cell growth between cells not administered the potential modulator and cells administered the potential modulator; and
- (f) identifying the potential modulator as a modulator of receptor protein tyrosine kinase function based on the difference in cell growth.

63. A method of identifying a modulator of receptor protein tyrosine kinase function, the method comprising:

- (a) modifying a three dimensional representation of a receptor protein tyrosine kinase having a compound, ligand, or ligand analog bound to it to provide a complex, wherein the three dimensional representations of the compound, ligand, or ligand analog and the receptor protein tyrosine kinase are defined by atomic structural coordinates;
- (b) determining a conformation of the complex with a favorable geometric fit and one or more favorable complementary interactions;
- (c) identifying a modified compound, ligand, or ligand analog that best fits the receptor protein tyrosine kinase as a potential modulator of receptor protein tyrosine kinase function;
- (d) administering the potential modulator to cells;
- (e) comparing the level of cell growth between cells not administered the potential modulator and cells administered the potential modulator; and

(f) identifying the potential modulator as a modulator of receptor protein tyrosine kinase function based on the difference in cell growth.

64. A method of identifying a modulator of receptor protein tyrosine kinase function, the method comprising:

- (a) providing a three dimensional representation of a compound, ligand, or ligand analog complexed with a receptor protein tyrosine kinase, where the three dimensional representations of the compounds, ligands, or ligand analogs and the receptor PTK are defined by atomic structural coordinates;
- (b) searching a data base for a compounds, ligand, or ligand analog similar to the complexed compound, ligand, or ligand analog using a compound searching computer program;
- (c) identifying the compound, ligand, or ligand analog similar to the complexed compound, ligand, or ligand analog as a potential modulator of receptor protein tyrosine kinase function;
- (d) administering the potential modulator to cells;
- (e) comparing the level of cell growth between cells not administered the potential modulator and cells administered the potential modulator; and
- (f) identifying the potential modulator as a modulator of receptor protein tyrosine kinase function based on the difference in cell growth.

65. A method of identifying a modulator of receptor protein tyrosine kinase function, the method comprising:

- (a) providing a three dimensional representation of a compound, ligand, or ligand analog complexed with a receptor protein tyrosine kinase, wherein the three dimensional representations of the compounds, ligands, or ligand analogs and the receptor protein tyrosine kinase are defined by atomic structural coordinates;
- (b) identifying the compound, ligand, or ligand analog as a potential modulator by replacing portions of the compound, ligand, or ligand analog complexed with the receptor protein tyrosine kinase with similar chemical structures from a data base using a compound construction computer program, wherein the representations of the compounds are defined by structural coordinates;
- (c) administering the potential modulator to cells;

- (d) comparing the level of cell growth between cells not administered the potential modulator and cells administered the potential modulator; and
  - (e) identifying the potential modulator as a modulator of receptor protein tyrosine kinase function based on the difference in cell growth.
66. A modulator of receptor protein tyrosine kinase function identified by the method of any one of claims 58-65.
67. A method of diagnosing a disease by identifying cells harboring a receptor protein tyrosine kinase with inappropriate activity, the method comprising:
- (a) administering a modulator of receptor protein tyrosine kinase function to cells;
  - (b) comparing a rate of cell growth by cells not administered the modulator and a rate of cell growth by cells administered the modulator; and
  - (c) diagnosing a disease by characterizing cells harboring a receptor protein tyrosine kinase with inappropriate activity by identifying those cells administered the modulator that exhibit a rate of cell growth different from the rate of cell growth by cells not administered the modulator.
68. A method of treating a disease associated with a receptor protein tyrosine kinase with inappropriate activity in a cellular organism, the method comprising:
- (a) administering a modulator of receptor protein tyrosine kinase function to the organism, where the modulator is in an acceptable pharmaceutical preparation; and
  - (b) activating or inhibiting the receptor protein tyrosine kinase function to treat the disease.
69. A crystal comprising a polypeptide, which includes an extracellular domain of a receptor protein tyrosine kinase; and a ligand bound to the extracellular domain.
70. The crystal of claim 69 further comprising a sulfated oligosaccharide bound to at least one of the ligand bound and the receptor protein tyrosine kinase.
71. The crystal of claim 70 wherein the sulfated oligosaccharide is a sulfated disaccharide, hexasaccharide, octasaccharide, decasaccharide, or dodecasaccharide.

72. The crystal of claim 70 wherein the sulfated oligosaccharide is sulfated mucooligosaccharide.
73. The crystal of claim 72 wherein the sulfated mucooligosaccharide is heparin.
74. The crystal of claim 70 comprising a FGF:FGFR:heparin ternary complex.
75. The crystal of claim 74 wherein the FGF:FGFR:heparin ternary complex is a FGF2:FGFR1:heparin ternary complex.
76. The crystal of claim 69 wherein the receptor protein tyrosine kinase is a fibroblast growth factor receptor and the ligand is a fibroblast growth factor.
77. The crystal of claim 76 wherein the receptor protein tyrosine kinase is fibroblast growth factor receptor 1 and the ligand is FGF2.
78. A three-dimensional representation of the structure of the polypeptide of claim 1, 8, 69, 70 or 73.
79. The three-dimensional representation of claim 78 in computer readable form.
80. A computer-readable medium having recorded thereon x-ray coordinate data for a crystal comprising a polypeptide which includes an extracellular domain of a receptor protein tyrosine kinase.
81. The computer-readable medium of claim 80, wherein the x-ray coordinate data is set forth in Table 1, 2, 3 or 6.
82. The computer-readable medium of claim 80, wherein the medium is selected from the group consisting of RAM, ROM, magnetic media, optical media, magnetic-optical media, floppy disks, hard disks, mini-disks, servers, CD, and DVD.
83. The computer-readable medium of claim 80, wherein when said medium is read by a machine programmed with instructions for using the data, the machine is capable of generating signals for analyzing molecular interaction.

84. The computer-readable medium of claim 83, wherein the signals are image signals that can depict a three-dimensional representation of the polypeptide or a portion thereof.
85. The computer-readable medium of claim 83, wherein the receptor protein tyrosine kinase is a fibroblast growth factor receptor; the crystal further comprises a fibroblast growth factor or portion thereof bound to the extracellular domain of the fibroblast growth factor receptor; and the image signals can depict a three-dimensional representation of a structure which includes an interface between the fibroblast growth factor receptor and the fibroblast growth factor.
86. The computer-readable medium of claim 87, further comprising a sulfated mucosaccharide bound to at least one of the fibroblast growth factor and the fibroblast growth factor receptor.
87. A computer-readable medium having recorded thereon x-ray coordinate data for a crystal comprising a polypeptide which includes a receptor binding core of a stem cell factor.
88. The computer-readable medium of claim 87, wherein the x-ray coordinate data is set forth in Table 4.
89. The computer-readable medium of claim 87, wherein the crystal further comprises a *c-kit* or portion thereof bound to the receptor binding core of the stem cell factor.